

REMARKS

Claims 1-53, 59-61, 63-66 and 78-86 are pending. Claims 4, 19, 35 and 36 are hereby amended as indicated above. Claims 5 and 36 are hereby canceled as redundant to claims 6 and 37, respectively, in light of amendments provided herein.

The Examiner has rejected claims 1-53, 59, 82, 83, and 85 under 35 USC §112, first paragraph for indefiniteness. Specifically, the Examiner asserts that the phrase "modulate the relative rate" found in claims 1, 30, 59, 82, 83, and 85 requires clarification, especially the terms "modulate" and "relative." In response, Applicants believe that this phrase is very clear in view of common definitions of the words "modulate" and "relative," and especially in the context of the claimed invention and the disclosure of the present application, as filed. Applicants' position presented below references claim 1, but is equally applicable to the rejection as applied to claims 30, 59, 82, 83, and 85.

As set forth in the specification of the present application (hereinafter, the "Specification"), multiplexed PCR reactions are PCR reactions in which two or more single amplification reactions are carried out in the same reaction vessel. As such, the two or more amplification reactions compete for resources, such as nucleotides and polymerase enzyme, present in the reaction vessel. If the reaction is not balanced, one PCR reaction of the two or more reactions within the same reaction vessel may out-compete other reactions within the same reaction vessel for necessary resources, resulting in disproportionate amplification reactions. Disproportionate amplification reactions do not accurately quantify the two or more target mRNA or DNA species. This point is made in the specification of the present patent application (see, for example, paragraphs [0052] through [0061] of the Specification and ABI PRISM 7700 Sequence Detection System User Bulletin #5, "Multiplex PCR with TaqMan VIC Probes", Applied Biosystems (1998/2001) (see, page 5, for example), which is

cited in paragraph [0052] of the Specification and which is of record in the present application.

The word “modulate” has a well-accepted definition that is entirely unambiguous, especially in the context of the present invention. Appendix A, attached hereto, provides dictionary definitions of “modulate” identified from a search of www.onelook.com. Various definitions are as follows:

“to adjust to or keep in proper measure or proportion” (Merriam-Webster OnLine);

“exert a controlling influence on; regulate” (Compact Oxford English Dictionary, www.askoxford.com);

“to adjust or adapt to a particular measure or proportion” (Wordsmythe);

“To adjust or adapt to a certain proportion; regulate or temper” (The American Heritage dictionary of the English Language: Fourth Edition (2000), from www.bartleby.com).

“to vary the strength, quality, or amount of (something)” (Cambridge Dictionary of American English); or

“to change something, such as an action or a process, to make it more suitable for its situation (Cambridge Advanced Learner’s Dictionary).

Likewise the word “relative” has a well-accepted definition that is entirely unambiguous, especially in the context of the present invention and claims; referring to the comparative rate of amplification of two amplicons in a multiplexed PCR reaction. Appendix B, attached hereto, provides dictionary definitions of the adjective “relative” identified from a search of www.onelook.com. Various definitions are as follows:

“measured or considered in comparison with each other or with something else” (Encarta);

“considered in relation or in proportion to something else” (Compact Oxford English Dictionary);

“in relation; relating” (Wordsmythe); or

“as judged or measured in comparison or proportion with something else”
(Cambridge Dictionary of American English).

In light of these common definitions of “modulate” and “relative,” there is absolutely no ambiguity in the phrase “to modulate the relative rate of production of a first amplicon by a first primer set and a second amplicon by a second primer set during the first and second amplification stages,” or like phrases found in claims 30, 59, 82, 83 and 85 in the context of the claims of the present application, the Specification and/or the prior art of record.

Claim 1 reads:

A multiplex PCR method, comprising the step of conducting a PCR amplification on a DNA sample in a PCR reaction mixture, wherein the PCR amplification is conducted in a first amplification stage and a second amplification stage, each amplification stage comprising one or more PCR cycles and each PCR cycle comprises a denaturing step, an annealing step and an elongation step that may be conducted at the same temperature as the annealing step, wherein the PCR amplification of the second amplification stage is conducted under different reaction conditions than the PCR amplification of the first amplification stage ***to modulate the relative rate of production of a first amplicon by a first primer set and a second amplicon by a second primer set during the first and second amplification stages*** (emphasis added).

Claims 30, 59, 82, 83 and 85 contain essentially, if not exactly the same language shown in bold-italic. As follows from the definitions and discussion, and, from the as-filed present application:

1. A PCR reaction produces an amplicon at a specific rate, as exemplified in the present application and throughout the literature at the time of filing of the present application. As a non-limiting example, C_t is one measure of the rate of accumulation of an amplicon.

2. A multiplexed reaction contains two or more PCR reactions, which produce two or more amplicons, which also is well-established in the art at the time of filing of the present application.
3. Each of the two or more PCR reactions in a multiplexed reaction produces its amplicon product at a rate relative to (see definitions of "relative" above) the rate of production of other amplicon product(s) in a given multiplexed reaction, as also shown in the present application and as recognized in the art at the time of filing of the present application. As a non-limiting example, each PCR reaction in a multiplexed reaction generates its own C_t (see, for example, Figures 2, 4, 12-16 and 18 of the present application).
4. To "modulate the relative rate of production" of two different amplicons in a multiplexed PCR reaction therefore means, in essence, to regulate, control, adjust, vary, *etc.* (see definitions of "modulate" provided above) the rate of production of a first amplicon by a first primer set relative to the rate of amplification of a second amplicon by a second primer set. This is described throughout the Specification and is what is claimed.

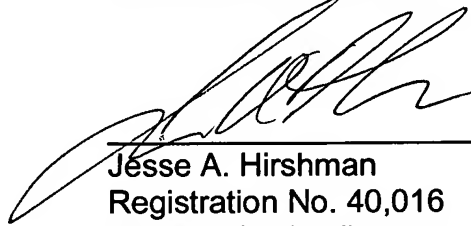
For the reasons set forth above, the meaning of the phrase "modulate the relative rate" is perfectly clear. Applicants respectfully request reconsideration of the rejection of claims 1-53, 59, 82, 83, and 85 under 35 USC §112, first paragraph for indefiniteness.

The Examiner has rejected claims 4, 5, 19, 35 and 36 under 35 USC §112, first paragraph for indefiniteness for recitation of the phrase, "derivative thereof." Applicants hereby amend claims 4, 19 and 35 to remove the phrase "derivative thereof" and hereby cancel claims 5 and 36 as redundant to claims 6 and 37, respectively once the phrase "derivative thereof" is removed from claims 5 and 36.

The Examiner has rejected claim 37 under 35 USC §112, first paragraph for indefiniteness for ending with the word "and" with no punctuation. Applicants hereby amend claim 37 to correct this typographic error.

In view of the amendments and remarks presented herein, Applicants believe that claims 1-4, 6-35, 37-53, 59-61, 63-66 and 78-86 define over the prior art of record and are in proper form for allowance. Applicants respectfully request allowance of claims 1-4, 6-35, 37-53, 59-61, 63-66 and 78-86.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'J. Hirshman', is written over a horizontal line.

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One entry found for **modulate**.

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Find

Main Entry: **mod·u·late**

Pronunciation: 'mä-j&-"lAt

Function: *verb*

Inflected Form(s): **-lat·ed; -lat·ing**

Etymology: Latin *modulatus*, past participle of *modulari* to play, sing, from *modulus* small measure, rhythm, diminutive of *modus* measure -- more at [METE](#)

transitive senses

1 : to tune to a key or pitch

2 : to adjust to or keep in proper measure or proportion :

TEMPER

3 : to vary the amplitude, frequency, or phase of (a carrier wave or a light wave) for the transmission of intelligence (as by radio); *also* : to vary the velocity of electrons in an electron beam

intransitive senses

1 : to play or sing with **modulation**

2 : to pass from one musical key into another by means of intermediary chords or notes that have some relation to both keys

3 : to pass gradually from one state to another

- **mod·u·la·tor** /-"lA-t&r/ *noun*

- **mod·u·la·to·ry** /-l&-"tOr-E, -"tor-/ *adjective*

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Compact Oxford English Dictionary

modulate

• **verb** 1 exert a controlling influence on; regulate. 2 vary the strength, tone, or pitch of (one's voice). 3 adjust the amplitude or frequency of (an oscillation or signal). 4 Music change from one key to another.

— DERIVATIVES **modulation** noun **modulator** noun.

— ORIGIN Latin *modulari* 'measure'.

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"dog" matches "guide dog"

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"dawg" matches "dog"

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modulate

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Syllables:

mod-u-late

Parts of speech:

[transitive verb](#) , [intransitive verb](#)



Part of Speech

transitive verb



Pronunciation

[ma jE](#) [let](#)

[mad](#) [yE](#) [let](#)

Inflected Forms

modulated, modulating, modulates

Definition

1. to adjust or adapt to a particular measure or proportion.

Synonyms

[adjust](#) (2) , [adapt](#) , [regulate](#) (2)

Crossref. Syn.

[proportion](#)

Similar Words

[vary](#) , [alter](#) , [modify](#) , [accommodate](#)

Definition

2. to vary the loudness, pitch, intensity, or tone of; esp. soften or tone down.

Example

When she realized the old woman was not deaf, she modulated her voice.

Synonyms

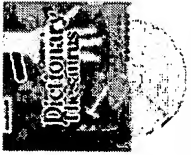
[adjust](#) (1) , [moderate](#) (1)

Crossref. Syn.

[tone](#) , [tone down](#)

Similar Words

[mute](#) , [tune](#) , [tone down](#) {[tone \(PHR\)](#)} , [soften](#) , [lower](#)¹ , [subdue](#)



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Definition

Synonyms

Similar Words

Definition

Synonyms

Similar Words

3. to vary the frequency, amplitude, phase, or the like of (an electromagnetic wave).

tune (2,4)

adjust , fine-tune

4. to tune to a particular musical key or pitch.

tune (1)

attune

Related Words

regulate



Part of Speech

intransitive verb

Definition

1. to shift from one musical key to another, as through chord progressions.

Definition

2. to vary the frequency, amplitude, phase, or the like of an electromagnetic wave.

Related Words

tone

Derived Forms

modulability, n. ; modulative, adj. ; modulator, n. ; modulatory, adj.

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modularized modulation

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modulate

SYLLABICATION: mod·u·late

PRONUNCIATION: mŏj' ə-lā't

VERB: Inflected forms: mod·u·lat·ed, mod·u·lat·ing, mod·u·lates

TRANSITIVE
VERB: 1. To adjust or adapt to a certain proportion; regulate or temper. 2. To change or vary the pitch, intensity, or tone of (one's voice or a musical instrument, for example). 3. *Electronics* a. To vary the frequency, amplitude, phase, or other characteristic of (electromagnetic waves). b. To vary (electron velocity) in an electron beam.

INTRANSITIVE
VERB: *Music* To move from one key or tonality to another by means of a melody or chord progression.

ETYMOLOGY: Latin *modulārī*, *modulāt-*, to measure off, to regulate, from *modulus*, diminutive of *modus*, measure. See *med-* in Appendix I.

OTHER FORMS: mod' u·la·bil' i·ty —NOUN

mod' u·la·tive, mod' u·la·to' ry (-lə-tōr' ē, -tōr' ē) —ADJECTIVE

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[modulation](#)

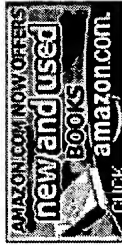
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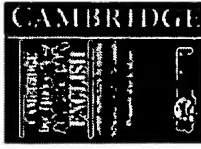


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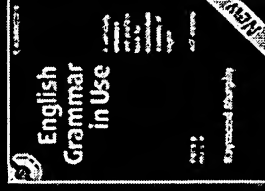
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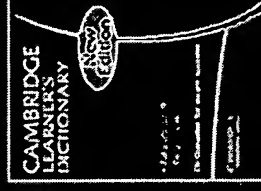
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Definition

modulate

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verb [T]

to vary the strength, quality, or amount of (something)

Teachers modulate the way they work in response to their students' needs.

Modulate your tone of voice when speaking in court.

(from [Cambridge Dictionary of American English](#))

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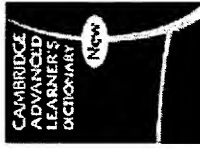
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Definition

modulate (CHANGE) [\[Show phonetics\]](#)

verb [T] FORMAL

to change something, such as an action or a process, to make it more suitable for its situation:

An elected committee will meet monthly to modulate the council's energy policy.

modulation [\[Show phonetics\]](#)

noun [C or U] FORMAL

(from [Cambridge Advanced Learner's Dictionary](#))

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relative

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grammar

relationship

▶ **relative**

relative atomic
mass

relative clause

relative
humidity

relative income
hypothesis

relative
performance
compensation

relative
permeability



rel·a·tive [réllätiv]

adjective

1. comparative: measured or considered in comparison with each other or with something else

- *discussing the relative merits of various methods of transportation*

2. changing with circumstances: not permanently fixed, but having a meaning or value that can only be established in relation to something else and will change according to circumstances or context

- "Big" and "small" are *relative terms*.

3. dependent on something: depending on or in proportion to something else

- *Payment will be relative to the value of the work done rather than the time taken to do it.*

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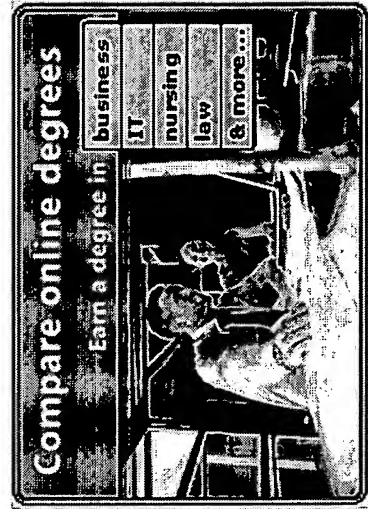
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relative
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relative pitch



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4. connected with something: connected with or referring to something

- *The lawyers now have most of the data relative to the case.*

5. GRAMMAR referring to previously used word: used to describe words, especially pronouns (relative pronouns) or clauses (relative clauses) that refer to another word previously used in the same sentence

6. MUSIC having identical key signatures: used to describe a key that has the same key signature as another, usually a minor key with the same sharps and flats as a major key, or vice versa

noun (plural rel·a·tives)

1. member of family: somebody who belongs to the same family by birth or through adoption or marriage

2. thing related to something else: one thing that is related to something else, especially a species that has developed from the same origin as another species

3. GRAMMAR relative word: a relative word, especially a pronoun, or a relative clause

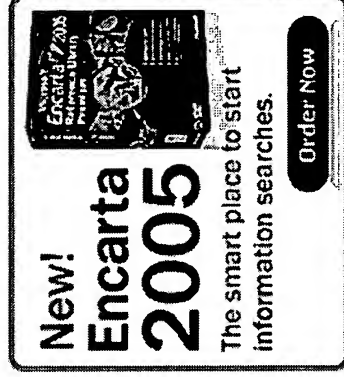
- rel·a·tive·ness *noun*

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relative

/rɛlətɪv/

• **adjective** **1** considered in relation or in proportion to something else. **2** existing or possessing a characteristic only in comparison to something else: *months of relative calm ended in April.* **3** Grammar (of a pronoun, determiner, or adverb) referring to an expressed or implied antecedent and attaching a subordinate clause to it, e.g. *which.* **4** Grammar (of a clause) attached to an antecedent by a relative word.

• **noun** **1** a person connected by blood or marriage. **2** a species related to another by common origin.

— PHRASES **relative to** **1** compared with or in relation to. **2** concerning.

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Syllables:

rel-a-tive

Parts of speech:

[noun](#) , [adjective](#)



Part of Speech



Pronunciation

noun

[reh](#) [lE](#) [ti](#)h

Definition

1. a person who is related to others through blood or marriage.

Synonyms

[kin](#) (2)

Crossref. Syn.

[relation](#) , [kin](#) , [kindred](#)

Definition

2. something that is dependent on something else for its specific form or meaning. (Cf. absolute.)

Synonyms

[condition](#) (3) , [contingency](#) (3)

Definition

3. in grammar, a relative pronoun, adjective, or adverb.

Related Words

[people](#) , [connection](#) , [brother](#) , [descendant](#) , [cognate](#) , [clan](#) , [family](#)



Part of Speech

adjective



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Definition

Synonyms

Similar Words

Definition

Example

Synonyms

Crossref. Syn.

Similar Words

Definition

1. in relation; relating.

comparative (3)

qualified , correlative , compared {compare (vt)}

2. meaningful only in relation to something else.

Some people argue that moral standards are relative. (Cf. absolute.)

dependent (2) , contingent (1) , provisory

comparative

conditional

3. in grammar, denoting or pertaining to a dependent clause or a word that introduces it, as in "She feared anyone whom she didn't understand," in which "whom" is a relative pronoun and "whom she didn't understand" is a relative clause.

Related Words

applicable , analogous , subordinate

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Definition

relative (COMPARED WITH)

[Show phonetics]

adjective [not gradable]

as judged or measured in comparison with something else

*We considered the **relative merits** of flying to Washington or taking the train.*

Relative to (= Considering) birthweight, the newborns were doing well.

(specialized) *In grammar, a **relative clause** is a clause in a sentence that cannot exist independently, begins with a relative pronoun, and describes a noun that comes before it:*

In the sentence "The movie that we saw was very good," "that we saw" is a relative clause.

(specialized) *In grammar, a **relative pronoun** is a pronoun such as "which," "who," or "that," used to begin a relative clause:*

In the sentence "The movie that we saw was very good," "that" is a relative pronoun.

relatively

[Show phonetics]

adverb [not gradable]

*The stereo was **relatively inexpensive**.*

(from *Cambridge Dictionary of American English*)

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